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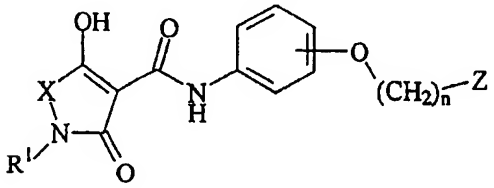
(54) Abstract Title
2-oxo, 4-hydroxy pyrroles and quinolines

(57) A compound which is a cyclic amide of formula (I):



I

wherein X is CHR^2 or $-C(R^3)=C(R^4)-$ wherein R^2 is H, C_1-C_6 alkyl or Ar and R^3 and R^4, together with the carbon atoms to which they are attached, form a benzene ring which is unsubstituted or substituted;
R^1 is H, C_1-C_6 alkyl, $-(CH_2)_nAr$ or an unsaturated carbocyclic group which is unsubstituted or substituted;
n is 1 to 10;
Ar is an unsaturated carbocyclic group or unsaturated heterocyclic group which is unsubstituted or substituted preferably benzothiophen; and
Z is tetrazole or CO_2R^5 wherein R^5 is H or C_1-C_6 alkyl; and the pharmaceutically acceptable salts thereof have activity as inhibitors of plasminogen activator inhibitor (PAI-1) for use in treating haemostatic or thrombotic disorders.

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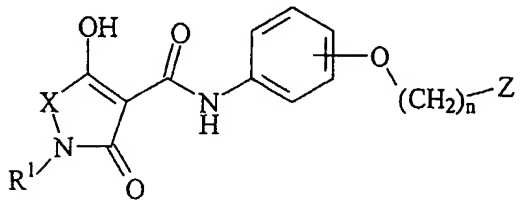
PHARMACEUTICAL COMPOUNDS

The present invention relates to compounds useful as inhibitors of plasminogen activator inhibitor (PAI-1), to their preparation and to pharmaceutical and veterinary compositions containing them.

Plasminogen activators (PAs) are serine proteases which control the activation of the zymogen, plasminogen, to the active enzyme plasmin. Plasmin is important in a variety of physiological and pathophysiological processes including fibrinolysis, atheroma, cancer, inflammation, wound healing and angiogenesis. Plasminogen is converted to proteolytically active plasmin by either tissue-type plasminogen activator (tPA) or urokinase-type plasminogen activator (Vassalli *et al*; J.Clin.Invest. 88, 1067-1072, 1991). Plasminogen activator inhibitor (PAI-1) is the major physiological inhibitor of plasminogen activators, and an increase in the level of PAI-1 has been proposed as a risk factor in thrombotic disease (Dawson *et al*, Atherosclerosis; 95, 105-117, 1992), and is associated with a poor prognosis in a variety of cancers (Pappot *et al*, Biol.Chem.Hoppe-Seyler; 376, 259-267, 1995). Inhibition of PAI-1 may therefore be of benefit in thromboembolic disease, atherosclerosis, inflammatory disease and tumour invasion, metastasis and tumour angiogenesis (Exp. Opin. Invest. Drugs 1997, 6(5), 539-554 (Charlton) and Nature Medicine vol. 4, no. 8, 923-928, 1998 (Bajou *et al*).

The present invention provides a compound which is a cyclic amide of formula (I)



I

wherein X is CHR^2 or $-C(R^3)=C(R^4)-$ wherein R^2 is H, C_1-C_6 alkyl or Ar and R^3 and R^4, together with the carbon atoms to which they are attached, form a benzene ring which is unsubstituted or substituted;

R^1 is H, C_1-C_6 alkyl, $-(CH_2)_nAr$ or an unsaturated carbocyclic group which is unsubstituted or substituted;

n is 1 to 10;

Ar is an unsaturated carbocyclic group or unsaturated heterocyclic group which is unsubstituted or substituted; and

Z is tetrazole or CO_2R^5 wherein R^5 is H or C_1-C_6 alkyl;

or a pharmaceutically acceptable salt thereof.

A C_1-C_6 alkyl group may be linear or branched. A C_1-C_6 alkyl group is typically a C_1-C_4 alkyl group, for example a methyl, ethyl, propyl, i-propyl, n-butyl, sec-butyl or tert-butyl group. A C_1-C_6 alkyl group which is substituted is typically substituted by one or more halogen atoms, for instance by 1, 2 or 3 halogen atoms. It may be a perhaloalkyl group, for instance trifluoromethyl.

A halogen is F, Cl, Br or I. Preferably it is F, Cl or I.

A C_1-C_6 alkylene chain is $-(CH_2)_m-$ wherein m is from 1 to 6. Typically m is from 1 to 4. Examples of C_1-C_6 alkylene include methylene (m=1), ethylene (m=2), propylene (m=3), butylene (m=4), pentylene (m=5) and hexylene (m=6).

A C_2-C_6 alkenylene chain is a hydrocarbon chain of 2 to 6 carbon atoms which includes at least one double bond (-CH=CH-). Examples include ethenylene, propenylene, butenylene, pentenylene and hexenylene.

A C_2-C_6 alkynylene chain is a hydrocarbon chain of 2 to 6 carbon atoms which includes at least one triple bond (-C≡C-). Examples include ethynylene, propynylene, butynylene, pentynylene and hexynylene. A preferred option is ethynylene.

A C_1-C_6 alkoxy group may be linear or branched. It is typically a C_1-C_4 alkoxy group, for example a methoxy, ethoxy, propoxy, i-propoxy, n-propoxy, n-butoxy, sec-butoxy or tert-butoxy group.

An unsaturated carbocyclic group is typically a C_5-C_{10} carbocyclic group which contains at least one unsaturated bond, for instance a C_6-C_{10} aryl group such as a phenyl or naphthyl group. A naphthyl group may be, for instance, naphth-1-yl or naphth-2-yl. The unsaturated carbocyclic group may be unsubstituted or substituted by one or more substituents, for instance one or more substitutents selected from halogen, OH, C_1-C_6 alkoxy, nitro, amino and C_1-C_6 alkyl which is unsubstituted or substituted, for instance by halogen (such as CF_3),

An unsaturated heterocyclic group is typically a 5 or 6-membered heterocyclic ring with at least one unsaturated bond, which contains one or more heteroatoms selected from N, S and O and which is optionally fused to a benzene ring or to a second such 5 or 6-membered heterocyclic ring. The heterocyclic group may be unsubstituted or substituted by one or more substituents, for instance one or more substituents selected from halogen, OH, C_1-C_6 alkoxy, nitro, amino and C_1-C_6 alkyl which is unsubstituted or substituted, for example by halogen (such as CF_3).

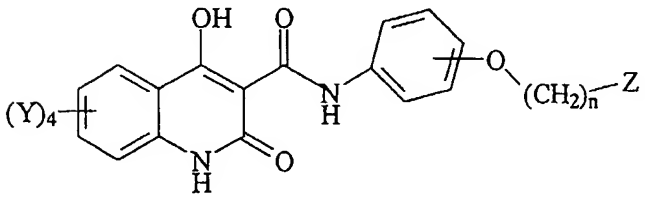
An unsaturated heterocyclic ring may be, for example, a furan, benzofuran, thiophene, benzothiophene, pyrrole, indole, isoindole, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, pyridine, quinoline, quinoxaline, isoquinoline,

thienopyrazine, pyran, pyrimidine, pyridazine, pyrazine, purine or triazine group. Preferably it is benzothiophene.

A benzene ring formed by R^3 and R^4 which is substituted may be substituted by one or more substituents at any available ring position. For instance, it may be mono-substituted, di-substituted or tri-substituted. Suitable substituents include those listed for group Y in formula (Ia) which follows.

In formula (I), the $-O-(CH_2)_n-Z$ moiety may be bonded to any of the available benzene ring positions. It may thus be ortho-, meta- or para-positioned relative to the amide moiety. Preferably it is bonded at the para-position.

In one aspect of the present invention the cyclic amide is of formula **Ia:**



Ia

wherein each Y, which may be the same or different, is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CN, CO_2R^5 wherein R^5 is as defined above for formula (I), $-O(CH_2)_pAr$, $-(Q)_pAr$, nitro, $N(R^5)_2$ wherein R^5 is as defined above, or C_1-C_6 alkyl which is unsubstituted or substituted by halogen, or is $-CONHR^6$, $-NHCOR^6$ or $-NHSO_2R^6$ wherein R^6 is C_1-C_6 alkyl or $(CH_2)_pAr$;

Q is a C_1-C_6 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene chain;

n is 1 to 10;

p is 0 to 6; and

Ar and Z are as defined above for formula (I):

Typically, in formula (Ia), at least one group Y is H. More typically two groups Y are H and the other two groups, which are the same or different, are other than H. Preferably three groups Y are H and one group Y is other than H.

When one group Y is other than H it may occupy any of the available positions 5, 6, 7 and 8 of the quinolone ring system. For instance, when it bears one substituent the quinolone may be 5-substituted , 6-substituted or 7-substituted. Preferably it is 6-substituted or 7-substituted, most preferably 6-substituted.

When two groups Y are other than H they are the same or different and occupy any two of the available positions 5, 6, 7 and 8 of the quinolone ring system. For instance, the quinolone may be 5,6-disubstituted, 6,7-disubstituted, 7,8-disubstituted, 5,7-disubstituted, 6,8-disubstituted or 5,8-disubstituted. Preferably it is 6,7-disubstituted.

When three groups Y are other than H they are the same or different and occupy any three of the available positions 5, 6, 7 and 8 of the quinolone ring system. For instance, the quinolone may be 5, 6, 7-trisubstituted, 5, 6, 8-trisubstituted or 6, 7, 8-trisubstituted.

In a preferred embodiment of formula (Ia):

one group Y is benzothiophene, halogen, nitro, amino, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, CN, CO_2R^5 or $NHCOR^6$ wherein R^5 is H or C_1-C_6 alkyl and R^6 is as defined above, or is $-O(CH_2)_pAr$, $-(CH_2)_pAr$, $-CONH(CH_2)_pAr$, $-NHSO_2Ar$ or $-C\equiv C-Ar$, wherein p is 0 or 1 and Ar is phenyl; and the other three groups Y are H;

n is 5 to 10; and

Z is CO_2H or tetrazole.

In this embodiment the group Y is preferably bonded at position 5, 6, or 7 of the quinolone ring, preferably position 6. When Y is benzothiophene it is typically benzothiophen-2-yl or benzothiophen-3-yl. The $-O(CH_2)_n$-Z chain is preferably bonded para- to the amide moiety on the ring-hand benzene ring.

In another preferred embodiment of formula (Ia):

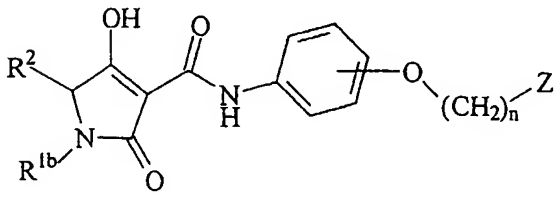
two groups Y are C_1-C_6 alkoxy, and the other two groups Y are H;

n is 5 to 10; and

Z is CO_2H or tetrazole.

In this embodiment the C_1-C_6 alkoxy groups are typically 6,7-di-C_1-C_6-alkoxy, more preferably 6,7-dimethoxy groups.

In another aspect of the present invention the cyclic amide is of formula (Ib):



Ib

wherein R^{1b} is C_1-C_6 alkyl or $-(CH_2)_pAr$ wherein Ar is as defined above for formula (I) and is unsubstituted or substituted by a group selected from C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, halogen, nitro, CO_2R^5 wherein R^5 is as defined above for formula (I), $-O(CH_2)_pAr$ or $-(CH_2)_pAr$ wherein Ar is as defined above, $NHCOR^6$ where R^6 is as defined above and C_1-C_6 alkyl which is unsubstituted or substituted by halogen;

R^2 is H, C_1-C_6 alkyl or Ar as defined above;

n is 1 to 10;

p is 0 to 6; and

Z is as defined for formula (I).

In a preferred embodiment of formula (Ib):

R^{1b} is C_1-C_6 alkyl or $-(CH_2)_pAr$ in which p is 0 or 1 and Ar is phenyl or naphthyl, Ar being unsubstituted or substituted by halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, nitro, CF_3, benzyl, phenyl, phenoxy, benzothiophene, -$NHCOR^6$ or $-COOR^6$ wherein R^6 is C_1-C_6 alkyl;

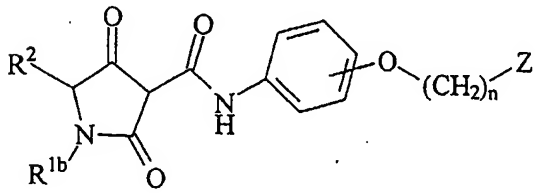
R^2 is H, C_1-C_6 alkyl or phenyl;

n is 5 to 10; and

Z is –COOH or tetrazole.

In this embodiment, when Ar is phenyl and is monosubstituted, it is preferably substituted at the 4-position. When Ar is phenyl and is di-substituted it is 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-disubstituted. Preferably it is 2,5-disubstituted. When the substituent is benzothiophene it may, for instance, be benzothiophen-2-yl or benzothiophen-3-yl.

The occurrence of keto-enol tautomerism may result in compounds of formula 1b existing in their keto form as shown in formula 1b'



Ib'

Examples of preferred compounds of the invention are:

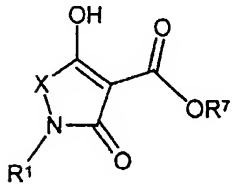
Compound Number	Chemical Name
1	6-Benzo[b]thiophen-3-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid {4-[7-(2H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide
2	6-Benzo[b]thiophen-2-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-

	carboxylic acid {4-[7-(2H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide
3	8-{4-[(6-Benzo[b]thiophen-3-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid
4	8-{4-[(6-Benzo[b]thiophen-3-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester
5	10-(4-{[6-(4-Chloro-phenyl)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-decanoic acid
6	6-(4-{[6-(4-Fluoro-benzoylamino)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-hexanoic acid
7	6-{4-[(4-Hydroxy-2-oxo-6-pentyl-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid
8	10-(4-{[6-(4-Chloro-benzyloxy)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-decanoic acid
9	10-(4-{[4-Hydroxy-6-(4-methoxy-phenoxy)-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-decanoic acid
10	7-{4-[(4-Hydroxy-7-nitro-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-heptanoic acid
11	8-{4-[(4-Hydroxy-6-iodo-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid
12	8-{4-[(5-Amino-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid
13	8-(4-{[6-(4-Chloro-benzenesulfonylamino)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-octanoic acid
14	6-{4-[(4-Hydroxy-2-oxo-7-trifluoromethyl-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid
15	7-{4-[(7-Acetylamino-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-heptanoic acid
16	8-(3-{[7-(4-Chloro-phenylcarbamoyl)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-octanoic acid
17	3-[4-(7-Carboxy-heptyloxy)-phenylcarbamoyl]-4-hydroxy-2-oxo-1,2-

	dihydro-quinoline-7-carboxylic acid methyl ester
18	8-[4-({7-[2-(4-Chloro-phenyl)-acetylamino]-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl}-amino)-phenoxy]-octanoic acid
19	6-{4-[(7-Cyano-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid
20	6-{4-[(4-Hydroxy-2-oxo-6-phenylethynyl-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid
21	8-{4-[(4-Hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid
22	8-{4-[(4-Hydroxy-2-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester
23	8-{4-[(4-Hydroxy-2-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid
24	8-(4-{[1-(4-Chloro-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester
25	8-(4-{[4-Hydroxy-1-(4-methoxy-phenyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester
26	8-(4-{[1-(4-Chloro-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid
27	8-{4-[(4-Hydroxy-2-oxo-1-p-tolyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester
28	8-{4-[(4-Hydroxy-2-oxo-1-p-tolyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid
29	8-(4-{[4-Hydroxy-1-(4-methoxy-phenyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid
30	2,4-Dioxo-1-p-tolyl-pyrrolidine-3-carboxylic acid {4-[7-(1H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide
31	1-(4-Chloro-phenyl)-2,4-dioxo-pyrrolidine-3-carboxylic acid {4-[7-(2H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide
32	1-(4-Methoxy-phenyl)-2,4-dioxo-pyrrolidine-3-carboxylic acid {4-[7-(2H-

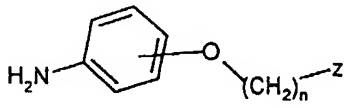
	tetrazol-5-yl)-heptyloxy]-phenyl}-amide
33	8-(4-{[1-(4-Nitro-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid
34	8-{4-[(4-Hydroxy-1-naphthalen-1-yl-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid
35	8-(4-{[4-Hydroxy-2-oxo-1-(4-trifluoromethyl-phenyl)-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid
36	8-(4-{[4-Hydroxy-1-(4-methyl-biphenyl-3-yl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid
37	8-(4-{[1-(4-Acetylamino-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid
38	8-(4-{[1-(4-Benzo[b]thiophen-2-yl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid
39	8-(4-{[1-(4-Cyclohexyl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid
40	8-(4-{[1-(4-Benzyl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid
41	3-{3-[4-(7-Carboxy-heptyloxy)-phenylcarbamoyl]-4-hydroxy-2-oxo-2,5-dihydro-pyrrol-1-yl}-benzoic acid methyl ester
42	8-(4-{[4-Hydroxy-2-oxo-1-(4-phenoxy-phenyl)-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-decanoic acid
43	8-{4-[(4-Hydroxy-5-methyl-2-oxo-1-p-tolyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid
44	1-[4-(4-Fluoro-benzyloxy)-phenyl]-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid {4-[7-(1H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide
45	8-{4-[(4-Hydroxy-2-oxo-1,5-diphenyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid
46	8-{4-[(1-Benzyl-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid

Compounds of formula (I) may be prepared by a process which comprises reacting a compound of formula (II):



II

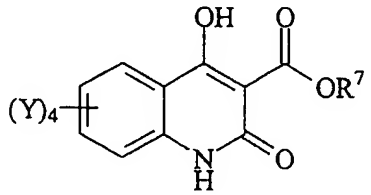
wherein R^7 is C_1-C_6 alkyl and X and R^1 are as defined above for formula (I), with a compound of formula (IV):



IV

wherein n and Z are as defined for formula (I) above, in an organic solvent at an elevated temperature. The solvent is preferably m-xylene, bromobenzene or N-methylpyrrolidine. A prefererred temperature is the reflux temperature of the solvent.

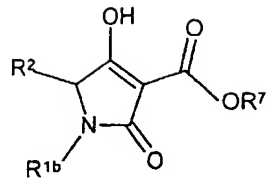
More specifically, the process comprises reacting a compound of formula (IIa)



IIa

wherein R^7 and Y are as defined above, with a compound of formula (IV) as defined above in an organic solvent at an elevated temperature to provide a compound of formula (Ia) as defined above.

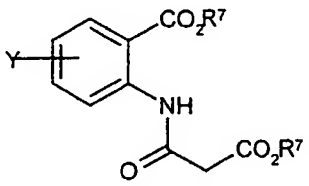
In another aspect the process comprises reacting a compound of formula (IIb)



IIb

wherein R^{1b}, R^2 and R^7 are as defined above, with a compound of formula (IV) as defined above in an organic solvent at an elevated temperature to provide a compound of formula (Ib) as defined above.

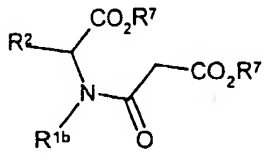
A compound of formula IIa may be prepared by Dieckmann cyclisation of a compound of formula IIIa:



IIIa

wherein Y and R^7 are defined as above. Typically this cyclisation reaction is performed in the presence of an alkoxide base in an alcohol at an elevated temperature. Preferably the reaction is performed using sodium methoxide in methanol at reflux.

A compound of formula (IIb) may be prepared by Dieckmann cyclisation of a compound of formula IIIb:



IIIb

wherein R^{1b}, R^2 and R^7 are defined as above. Typically this cyclisation reaction is performed in the presence of an alkoxide base in an alcohol at an elevated temperature. Preferably the reaction is performed using sodium methoxide in methanol at reflux.

Compounds of formulae (IIIa), (IIIb) and (IV) are prepared by standard experimental procedures and are described in the reference examples which follow.

If desired one compound of formula (I) may be converted into another compound of formula (I). For example an alkyl ester, for example a methyl or ethyl ester, may be converted into the corresponding carboxylic acid by acid or alkaline hydrolysis. In another example a compound of formula (I) containing a carboxylic acid group may be converted into the corresponding ester by esterification, for instance, by treatment with an appropriate alcohol.

A cyclic amide of formula (I) may be converted into a pharmaceutically acceptable salt, and a salt may be converted into the free cyclic amide, by conventional methods. Salts may be formed by compounds containing a carboxylic acid or tetrazole function. Suitable salts include those derived from pharmaceutically acceptable inorganic bases. Examples of such bases include ammonia and carbonates, hydrogencarbonates and hydroxides of group I and group II metals such as sodium, potassium, magnesium and calcium.

The cyclic amides of formula (I) and their pharmaceutically acceptable salts and esters (referred to hereinafter as the "present compounds") have utility as inhibitors of PAI-1. They may thus be used to treat a disease or disorder associated with elevated or inappropriate levels of PAI.

Elevated levels of PAI-1, by reducing the net endogenous fibrinolytic capacity, can contribute to the pathogenesis of various thrombotic disorders including coronary artery disease, acute myocardial infarction, unstable angina, deep vein thrombosis and recurrent venous thromboembolism (Declerck *et al*; J.Intern.Med. 236,425-432, 1994. Aznar *et al*; Haemostasis 24,243-251,1994. Gray *et al*; Haemostasis, 73, 261-267, 1995). The present compounds therefore can act as inhibitors of the tPA/PAI-1 interaction. The present compounds can be used in the treatment of haemostatic disorders. A human or animal, e.g. a mammal, can therefore be treated by a method comprising administration of a therapeutically effective amount of a cyclic amide of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof.

Tissue plasminogen activator (tPA) is used as a thrombolytic agent in the treatment of thrombotic disorders. The efficacy of the tPA in this role may be enhanced if it is administered together with a PAI-1 inhibitor. A human or animal, e.g. a mammal, can therefore be treated by a method comprising the combined administration of a therapeutically effective amount of tPA and a therapeutically effective amount of any one of the present compounds. The present invention also provides products containing a cyclic amide of formula (I) or a pharmaceutically acceptable salt or ester thereof and tPA as a combined preparation for simultaneous, separate or sequential use in the treatment of thrombotic disorders, for example where there is inappropriate PAI-1 activity. In such products the present compound is formulated for oral or parenteral (intravenous, intramuscular or subcutaneous) administration and the tPA is formulated for intravenous administration.

As one example, during acute myocardial infarction (MI) one of the present compounds may be administered to a patient together with tPA to enhance the efficacy of the tPA treatment. As a further example, early re-occlusion following treatment of a patient with tPA may be prevented by the post-MI administration of one of the present compounds.

The present compounds have been tested in a PAI-1 functional assay. In this assay, a compound is incubated with PAI-1 prior to addition to the tPA assay system. Inhibition of PAI-1 by compounds of Formula (I) prevents inhibition by PAI-1 of the enzymatic activity of tPA. In turn, tPA cleaves the chromogenic substrate Pefachrome (CH_3SO_2-D-HHT-Gly-Arg-pNA) (Centerchem, Inc) producing pNA (p-nitroaniline) which is detected spectrophotometrically at 405 nm (K.Nilsson *et al*, Fibrinolysis (1987) 1, 163-168). This is referred to as the chromogenic assay and the results of the assay are reported below.

A selection of the present compounds has also been tested in a clot lysis assay which can quantify the PAI-1 inhibitory activity of the compounds by measuring the rate of fibrinolysis (Ehnebom J, Kristianssen C, Bjorquist P, Deinum J, Bostrum S. Thrombosis and Haemostasis, 1993, 69, 1330a). This is referred to as the fibrin plate assay and is described in more detail below.

The present compounds may be administered in a variety of dosage forms, for example orally such as in the form of tablets, capsules, sugar- or film-coated tablets, liquid solutions or suspensions or parenterally, for example intramuscularly, intravenously or subcutaneously. The present compounds may therefore be given by injection or infusion.

The dosage depends on a variety of factors including the age, weight and condition of the patient and the route of administration. Typically, however, the dosage adopted for each route of administration when a compound of the invention is administered alone to adult humans is 0.001 to 10 mg/kg, most commonly in the range of 0.01 to 5 mg/kg, body weight. Such a dosage may be given, for example, from 1 to 5 times daily by bolus infusion, infusion over several hours and/or repeated administration.

When one of the present compounds is administered in combination with tPA to adult humans, the dosage adopted for each route of administration is typically from 0.001 to 10 mg, more typically 0.01 to 5 mg per kg body weight for a compound of the invention and from 5 to 500 mg administered intravenously for the tPA. A suitable dosage regimen for the tPA is 100 mg given intravenously over 3 hours as follows: 10% of the total dose as an i.v. bolus over 1-2 minutes, 50% of the total dose as an infusion over 1 hour, 40% of the total dose as an infusion over the subsequent 2 hours.

A cyclic amide of formula (I) or a pharmaceutically acceptable salt or ester thereof is formulated for use as a pharmaceutical or veterinary composition also comprising a pharmaceutically or veterinarily acceptable carrier or diluent. The compositions are typically prepared following conventional methods and are administered in a pharmaceutically or veterinarily suitable form. An agent for use as an inhibitor of PAI-1 comprising any one of the present compounds is therefore provided.

For example, the solid oral forms may contain, together with the active compound, diluents such as lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants such as silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; binding agents such as starches, arabic gums, gelatin,

methylcellulose, carboxymethylcellulose, or polyvinyl pyrrolidone; disintegrating agents such as starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs, sweeteners; wetting agents such as lecithin, polysorbates, lauryl sulphates. Such preparations may be manufactured in known manners, for example by means of mixing, granulating, tabletting, sugar coating, or film-coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carrier, for example, saccharose or saccharose with glycerol and/or mannitol and/or sorbitol. In particular, a syrup for diabetic patients can contain as carriers only products, for example sorbitol, which do not metabolise to glucose or which only metabolise a very small amount to glucose. The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose or polyvinyl alcohol.

Suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier such as sterile water, olive oil, ethyl oleate, glycols such as propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. Some of the present compounds are insoluble in water. Such compounds may be encapsulated within liposomes.

The present invention will be further illustrated in the following examples.

Reference Example 1: Preparation of Compounds of General Formula (IV)

Reference Example 1A: 8-(4-Amino-phenoxy)-octanoic acid methyl ester

To a stirring suspension of 8-bromooctanoic acid (4.0g) and trimethyloxonium tetrafluoroborate (2.92g) in dichloromethane (100mL) was added diisopropylethyl amine

(3.44mL). After stirring for 18 hours and aqueous work-up, 8-bromo-octanoic acid methyl ester was isolated as a yellow liquid (4.15g, 97%).

To a solution of 4-nitrophenol (3.99g) in N,N-dimethylformamide (70mL) was added sodium hydride (60% dispersion in mineral oil, 1.41g) under N_2. Once effervescence was completed, 8-bromo-octanoic acid methyl ester (7.64g) was added and the reaction mixture heated to 60°C. A catalytic amount of tetrabutylammonium iodide was added. After 18 hours the reaction mixture was cooled, diluted with ethyl acetate, washed with sodium carbonate solution and brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a yellow solid. This was recrystallised from ethyl acetate/hexane to yield 8-(4-nitro-phenoxy)-octanoic acid methyl ester as a yellow solid (6.17g)

To a suspension of 8-(4-nitro-phenoxy)-octanoic acid methyl ester (4.19g) in methanol (40mL) was added concentrated HCl (6.5mL) and iron (3.41g) and the reaction mixture was heated to 80°C. After 45 minutes the reaction mixture was cooled, diluted with ethyl acetate and washed with sodium carbonate solution. A precipitate appeared and this was removed by filtration. The organic layer was collected, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the title compound as a dark oil (4.0g)

In an analogous manner the following compounds of formula (IV) may be prepared;

6-(4-Amino-phenoxy)-hexanoic acid methyl ester;

7-(4-Amino-phenoxy)-heptanoic acid methyl ester;

10-(4-Amino-phenoxy)-decanoic acid methyl ester;

8-(3-Amino-phenoxy)-octanoic acid methyl ester.

Reference Example 1B: 4-[7-(2H-Tetrazol-5-yl)-heptyloxy]-phenylamine

1,7-Dibromoheptane (83.91g) was added to a suspension of potassium carbonate (44.95g) and 4-nitrophenol (15.08g) in N,N-dimethylformamide (200mL) .The reaction mixture as stirred at 30°C for 3 hours. N,N-dimethylformamide was removed *in vacuo* and the residue was then dissolved in ethyl acetate, washed with sodium carbonate solution and brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield an oil. This was purified using flash chromatography (eluting with hexane/ethyl acetate, 4:1) and then recrystallised from dichloromethane/hexane to yield 1-(7-bromo-heptyloxy)-4-nitro-benzene as a cream solid (19.0g)

To a stirring solution of 1-(7-Bromo-heptyloxy)-4-nitro-benzene (10.17g) in ethanol (70mL) and water (30mL) was added potassium cyanide (5.45g) and the reaction mixture was heated to reflux. After 1 hour the reaction mixture was cooled, diluted with ethyl acetate, washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield 8-(4-nitro-phenoxy)-octanenitrile as a yellow oil which crystallised slowly (6.27g).

A mixture of 8-(4-nitro-phenoxy)-octanenitrile (5.64g), triethylamine hydrochloride (2.96g), sodium azide (2.80g) and ammonium chloride (1.21g) was heated to 120°C for 18 hours. The reaction mixture was then cooled, poured onto water, acidified to pH 1 with HCl (2M), and then extracted into ethyl acetate. The organic phase was extracted with sodium hydroxide solution and the alkaline extract was washed with ether. The alkaline extracts were then acidified, and the organics extracted with ethyl acetate, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the title compound as a yellow solid (4.26g).

Reference Example 2: Preparation of Compounds of General Formula (IIIa)

Reference Example 2A: 4,5-dimethoxy-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester

4,5-Dimethoxyanthranilic acid (5.0 g,) was dissolved in dichloromethane (80 ml) and methanol (20 ml) and cooled in icebath. 2M TMS-CHN_2 in hexanes (15 ml) was diluted with dichloromethane (15 ml) and added with stirring. Acetic acid was then added to quench unreacted TMS-CHN_2. The reaction mixture was washed with $NaHCO_3$ solution and dried over Na_2SO_4. After filtration of the Na_2SO_4, the filtrate was concentrated *in vacuo* and the resulting oil purified by flash column chromatography to yield the desired methyl ester (3.0 g).

The above methyl ester (2.8g) and triethylamine (1.2 equivs) were dissolved in dichloromethane (150 ml) and cooled in an icebath. Malonyl chloride (1.8 equivalents) in dichloromethane (100 ml) was added dropwise with stirring. The reaction mixture was concentrated *in vacuo*, redissolved in EtOAc and washed with 1N HCl (2x), H_2O (1x), saturated $NaHCO_3$ (2x), H_2O (1x), saturated NaCl (1x) and dried over Na_2SO_4. After filtration of the Na_2SO_4 the filtrate was concentrated *in vacuo* and the resulting residue purified flash column chromatography to yield the title compound.

The following compounds of Formula IIIa were prepared in an analogous fashion using the appropriate anthranilic acid, which is either available commercially or prepared using literature methods.

4-Cyano-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester ;

2-(2-methoxycarbonyl-acetylamino)-4-trifluoromethyl-benzoic acid methyl ester;

2-(2-methoxycarbonyl-acetylamino)-4-nitro-benzoic acid methyl ester;

2-(2-Methoxycarbonyl-acetylamino)-terephthalic acid dimethyl ester;

4-Acetylamino-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester;

4-[2-(4-Chloro-phenyl)-acetylamino]-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester;

2-(2-Methoxycarbonyl-acetylamino)-N-phenyl-terephthalamic acid methyl ester;

Reference Example 2B: 5-Benzo[b]thiophen-3-yl-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester

A solution of bromine (2.36g) in carbon tetrachloride (5mL) was added slowly with stirring to a solution of benzo[b]thiophene (2.00g) in carbon tetrachloride (10mL) maintained at 15°C. After 20 hours the reaction mixture was washed with sodium bicarbonate solution, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield 3-bromo-benzo[b]thiophene as a pale oil (3.04g)

To a solution of 3-bromo-benzo[b]thiophene (2.04g) in dry ether (20mL) at -78°C under N_2 was added carefully a 1.6M solution of nBuLi in hexanes (7.8mL). After 30 minutes a solution of tributyl borate (5.17mL) in ether (30mL) was added at -78°C carefully. The reaction mixture was allowed to warm very slowly to room temperature and then stired for 2 days. The reaction mixture was then diluted with ether, and dilute HCl added. The organic layer was collected, extracted with sodium hydroxide solution (2M, 3X), acidified and then re-extracted with ether. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to yield 3-benzo[b]thiopheneboronic acid as a pale pink solid which was recrystallised from ethyl acetate (798mg).

To a solution of concentrated HCl (2mL) and methyl anthranilate (4.23g) in water (5mL) cooled to 0°C, was added iodine monochloride (5.0g) and concentrated HCl (2.8mL) in water, maintaining the low temperature. After stirring for 18 hours the reaction mixture was filtered yielding a brown solid. This was dissolved in dichloromethane, treated with activated carbon, filtered and then dried ($MgSO_4$) and the solvent removed *in vacuo* to yield 2-amino-5-iodo-benzoic acid methyl ester as a dark solid (5.46g).

To a solution of 2-amino-5-iodo-benzoic acid methyl ester (5.46g) in dichloromethane (75mL) at 0°C was added triethylamine (3.02mL), and a solution of methyl malonyl chloride (2.33mL) in dichloromethane (10mL) dropwise. After 3 hours an additional 1.0mL of methyl malonyl chloride and (1.5mL) of triethylamine was added. After one further hour the reaction mixture was diluted with dichloromethane, washed with sodium bicarbonate solution, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a pale solid which was recrystallised from ethyl acetate/hexane to yield 5-iodo-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester as an off-white solid (5.41g)

A mixture of 5-iodo-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester (910mg) and 3-benzo[b]thiopheneboronic acid (620mg) was stirred at room temperature in 1,2-dimethoxyethane (33mL). To this was added a solution of sodium carbonate (892mg) in water (13mL). The mixture was degassed with N_2 for 5 minutes. Dichlorobis(triphenylphosphine)palladium (II) (37mg) was added and the reaction mixture was heated to reflux for 5 minutes. The reaction mixture was cooled, diluted with ethyl acetate, washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to

yield a red solid. This was purified using flash chromatography (ethyl acetate/hexane 1:1) to yield the title compound as a pale orange oil (495mg)

Reference Example 2C: 5-(4-Fluoro-benzoylamino)-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester

To a solution of 5-amino-2-nitrobenzoic acid (5.140 g, 28 mmol) in 50 mL of 20% methanol/dichloromethane mixture was added slowly (trimethylsilyl)diazomethane (2.0M in hexanes, 21.1 mL, 42.2 mmol) in 10 mL of dichloromethane. When the reaction was completed, 3 mL of acetic acid was added to quench the excess diazomethane reagent. Methanol (100 mL) was added to the reaction solution in order to remove unreacted acetic acid as an azeotropic mixture under reduced pressure. The protected acid was obtained as brown solid product(92%) and was used in the subsequent step without any purification stage.

To a solution of the above crude protected acid (0.506, 2.58 mmol) in 11 mL of dichloromethane at 0 °C was added triethylamine (0.287 g, 2.84 mmol). To this was added 4-flluorobenzoyl chloride (0.964 g, 5.96 mmol) and the reaction mixture stirred for 8 hours. The reaction was quenched with water and extracted with EtOAc (X 3, 30 mL). The organic layer was dried and concentrated to yield crude product.
To a nitrogen-flushed Parr-bottle was added above intermediate (2.512 g, 7.9 mmol) and 120 mL of anhydrous ethanol. To this solution was then added 10%Pd/carbon catalyst (0.250 g). The reduction was carried out at 40 psi on the Parr apparatus for 2-3 h. The black crude product solution was filtered through a pad of celite under vacuum. The

filtrate was concentrated under reduced pressure afford 2-amino-5-(4-fluoro-benzoylamino)-benzoic acid methyl ester in 83% yield.

Reaction with methyl malonyl chloride was performed as described in Reference Example 2A to yield the title compound.

Reference Example 2D: 2-(2-methoxycarbonyl-acetylamino)-5-pentyl-benzoic acid methyl ester

A mixture of 5-iodo-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester (2.0 g, 5.3 mmol), 1-pentyne (0.8 mL, 7.9 mmol), cuprous iodide (100 mg, 0.53 mmol), triethylamine (3.7 mL, 26.5 mmol) and tetrakis(triphenylphosphine)palladium (612 mg, 0.53 mmol) in dichloromethane (100 mL) was heated to reflux under argon for 1h. The solution was cooled and concentrated on a rotary evaporator. The residue was adsorbed onto silica gel and purified via flash chromatography to give 2-(2-methoxycarbonyl-acetylamino)-5-pent-1-ynyl-benzoic acid methyl ester.

To a mixture of 2-(2-methoxycarbonyl-acetylamino)-5-pent-1-ynyl-benzoic acid methyl ester (1.32 g, 4.16 mmol) in ethanol (50 mL) and ethyl acetate (10 mL) was added 10% palladium on carbon (300 mg), and the mixture was stirred under an atmosphere of hydrogen (via a balloon) overnight. The catalyst was removed by filtration and the solvent was removed on a rotary evaporator to give the title compound.

Referece example 2E 2-(2-Methoxycarbonyl-acetylamino)-5-phenylethynyl-benzoic acid methyl ester

A mixture of 2-amino-5-iodo-benzoic acid methyl ester (10 g, 36 mmol), phenylacetylene (5.4 g, 53 mmol), cuprous iodide (1.0 g, 5.3 mmol) and triethylamine

(25 mL, 180 mmol) in dichloromethane (100 mL) was degassed with nitrogen for 5 min. Tetrakis(triphenylphosphine)palladium (200 mg, catalytic) was added and the mixture was stirred under argon overnight, then heated to reflux for 3 h. The residue was adsorbed onto silica gel and purified via flash chromatography to give 2-amino-5-phenylethynyl-benzoic acid methyl ester.

Reaction with methyl malonyl chloride was performed as described in Reference Example 2A to yield the title compound.

Reference Example 2F 5-(4-Chloro-benzyloxy)-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester

To a dried flask was added 5-hydroxy-2-nitrobenzaldehyde (60 mmoles, 10.03g) and anhydrous DMF (50 ml). 4-Chlorobenzyl chloride (55 mmoles, 8.85 g, 7.02ml) was added to the stirred reaction mixture and the mixture stirred for 5 minutes resulting in a homogenous mixture. Anhydrous potassium carbonate (65 mmoles, 8.98g) was added in one lot. The reaction mixture was then heated to 100 °C for 4 hours. The reaction mixture was allowed to cool to room temperature and poured into ethyl acetate (400 ml) and washed with saturated aqueous potassium carbonate (5 x 200 ml) and saturated sodium chloride solution (3 x 250 ml). The organic layer was dried over anhydrous sodium sulphate, filtered, and evaporated to dryness to yield 5-(4-chlorobenzyloxy)-2-nitrobenzaldehyde.

To a mixture of 4-(4-chlorobenzyloxy)-2-nitrobenzaldehyde (10 mmole, 2.915 g) and anhydrous pyridine (20 ml) was added solid tetra-n-butylammonium permanganate (7 mmoles, 2.53 g during the course of 15 minutes. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was poured in to ethyl acetate (100

ml) and 6M hydrochloric acid (100 ml). Solid sodium hydrogen sulphite was added to destroy excess oxidizing agent, and the layers were separated. The aqueous layer was further washed with ethyl acetate (2 x 100 ml). The combined organic layers were dried (magnesium sulphate) and the solvent removed in vacuo to yield 4-(4-chlorobenzyloxy)-2-nitrobenzoic acid (2.80g) as an orange solid.

Esterification was achieved using (trimethylsilyl) diazomethane to yield methyl 4-(4-chlorobenzyloxy)-2-nitrobenzoate. Reduction of the nitro group was performed using iron powder according to the literature (Synthetic Communications 1992, 22:22, 3189-3195) Reaction with methyl malonyl chloride was performed as described previously to yield the title compound.

Reference Example 2G 2-(2-Methoxycarbonyl-acetylamino)-5-(4-methoxy-phenoxy)-benzoic acid methyl ester

A dried flask was charged with 37%w/w potassium fluoride on basic alumina (2.5g/g 12.41 g), anhydrous acetonitrile (87 ml), methyl 5-chloro-2-nitrobenzoate (8.63g, 40 mmole) and 4-methoxyphenol (40 mmoles, 4.96 g). The reaction was heated to reflux for 25 hours. The reaction mixture was allowed to cool to room temperature and filtered through a sintered glass funnel, washing the recovered alumina with diethyl ether (3 x 50 ml). The combined organic solution was washed with cold water (2 x 200 ml) and saturated potassium chloride solution (200 ml). The organic solution was dried over sodium sulphate, filtered and evaporated in vacuo to give 5.737 g of the desired 5-(4-methoxy)-2-nitrobenzoate. Reduction of the nitro group and reaction with methyl malonyl chloride was performed as described previously to yield the title compound.

Reference Example 3: Preparation of Compounds of General Formula (IIa)

Reference Example 3A. 6-Benzo[b]thiophen-3-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester

To a freshly prepared solution of sodium methoxide (from sodium, 60mg, in dry methanol, 5mL), was added a solution of 5-benzo[b]thiophen-3-yl-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester (495mg) in methanol (3mL). The reaction mixture was heated to reflux for 90 minutes and then cooled and poured onto ice/dilute HCl. The resulting precipitate was collected by filtration and air dried to yield the title compound as a white solid (310mg)

In an analogous manner the following compounds of formula (IIa) may be prepared from the appropriate compound of formula (IIIa)

4-Hydroxy-6-iodo-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester was prepared from 5-iodo-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester;

4-Hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester was prepared from 4,5-dimethoxy-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester;

7-Cyano-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester was prepared from 4-cyano-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester;

4-Hydroxy-2-oxo-7-trifluoromethyl-1,2-dihydro-quinoline-3-carboxylic acid methyl ester was prepared from 2-(2-methoxycarbonyl-acetylamino)-4-trifluoromethyl-benzoic acid methyl ester;

4-Hydroxy-2-oxo-6-phenylethynyl-1,2-dihydro-quinoline-3-carboxylic acid methyl ester was prepared from 2-(2-methoxycarbonyl-acetylamino)-5-phenylethynyl-benzoic acid methyl ester;

4-Hydroxy-2-oxo-6-pentyl-1,2-dihydro-quinoline-3-carboxylic acid methyl ester was prepared from 2-(2-methoxycarbonyl-acetylamino)-5-pentyl-benzoic acid methyl ester ;

4-Hydroxy-7-nitro-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester was prepared from 2-(2-methoxycarbonyl-acetylamino)-4-nitro-benzoic acid methyl ester;

6-(4-Fluoro-benzoylamino)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester was prepared from 5-(4-fluoro-benzoylamino)-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester;

4-Hydroxy-2-oxo-7-phenylcarbamoyl-1,2-dihydro-quinoline-3-carboxylic acid methyl ester was prepared from 2-(2-methoxycarbonyl-acetylamino)-N-phenyl-terephthalamic acid methyl ester;

4-Hydroxy-2-oxo-1,2-dihydro-quinoline-3,7-dicarboxylic acid dimethyl ester was prepared from 2-(2-methoxycarbonyl-acetylamino)-terephthalic acid dimethyl ester;

7-Acetylamino-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester was prepared from 4-acetylamino-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester;

7-[2-(4-Chloro-phenyl)-acetylamino]-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester was prepared from 4-[2-(4-chloro-phenyl)-acetylamino]-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester;

6-(4-Chloro-benzyloxy)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester was prepared from 5-(4-chloro-benzyloxy)-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester;

4-Hydroxy-6-(4-methoxy-phenoxy)-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester was prepared from 2-(2-methoxycarbonyl-acetylamino)-5-(4-methoxy-phenoxy)-benzoic acid methyl ester.

Reference Example 3B. 6-Benzo[b]thiophen-2-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester

A mixture of 5-iodo-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester (1.06g) and benzo[b]thiophene-2-boronic acid (commercially available, 500mg) was stirred at room temperature in 1,2-dimethoxyethane (35mL). To this was added a solution of sodium carbonate (931mg) in water (14mL). The mixture was degassed with N_2 for 5 minutes. Dichlorobis(triphenylphosphine)palladium (II) (38mg) was added and the reaction mixture was heated to reflux for 30 minutes. The reaction mixture was cooled, diluted with ethyl acetate, washed with brine, and then acidified (HCl, 2N) and the solid which persisted was collected by filtration and washed with water and ethyl acetate (600mg)

In an analogous manner the following compounds of formula (IIa) may be prepared;

6-(4-Chloro-phenyl)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester was prepared from 5-iodo-2-(2-methoxycarbonyl-acetylamino)-benzoic acid methyl ester and 4-chlorobenzeneboronic acid.

Reference Example 3C. 6-(4-Chloro-benzenesulfonylamino)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester

To a stirred solution of compound 4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester (2.199 g, 10 mmol) in 10 mL of conc. nitric acid at 0 °C was added 10mL of conc. sulphuric acid. After stirring overnight at room temperature, the reaction mixture was poured onto ice/water. A precipitate was produced which was collected by filtration to yield the desired product, 4-hydroxy-6-nitro-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester (70%)

To a stirred solution of 4-hydroxy-6-nitro-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester (1.320 g, 5 mmol) in methanol (15 mL) under nitrogen was added 10% Pd/carbon (120 mg). To the above black solution was added ammonium formate (2.140 g, 23 mmol) carefully. The reaction mixture was stirred at RT for 6 hrs. The crude mixture was passed through a pad of celite under reduced pressure and washed many times with methanol. The filtrate was concentrated to afford compound 6-amino-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester (51%)

To a solution of 6-amino-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester (0.423 g, 1.81 mmol) in DMF (6 mL) was added triethylamine (0.219 g, 2.17 mmol). 4-Chlorobenzenesulphonyl chloride (1.3 equivalents) was then added and the reaction mixture was heated to 60-75 °C for 4 h. Reaction was cooled to RT and water was added to yield a precipitate which was collected by filtration to yield the title compound.

Example 1: Preparation of Compounds of General Formula (Ia)

8-{4-[(6-Benzo[b]thiophen-3-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester

A mixture of 6-benzo[b]thiophen-3-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester (0.31g) and 8-(4-amino-phenoxy)-octanoic acid methyl ester (281mg) in m-xylene (5mL) was heated to reflux under N_2. After 3 hours the reaction mixture was cooled and the precipitate was collected by filtration and washed with ethyl acetate and ethanol to yield the title compound as a white solid (0.42g).

In an analogous manner the following compounds of formula (Ia) may be prepared by using the appropriate compounds of formula (IIa) and the appropriate compound of formula (IV).

6-Benzo[b]thiophen-3-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid {4-[7-(2H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide;

6-Benzo[b]thiophen-2-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid {4-[7-(2H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide;

10-(4-{[6-(4-Chloro-phenyl)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-decanoic acid methyl ester;

6-(4-{[6-(4-Fluoro-benzoylamino)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-hexanoic acid methyl ester;

6-{4-[(4-Hydroxy-2-oxo-6-pentyl-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid methyl ester;

10-(4-{[6-(4-Chloro-benzyloxy)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-decanoic acid methyl ester;

10-(4-{[4-Hydroxy-6-(4-methoxy-phenoxy)-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-decanoic acid methyl ester;

7-{4-[(4-Hydroxy-7-nitro-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-heptanoic acid methyl ester;

8-{4-[(4-Hydroxy-6-iodo-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester;

8-(4-{[6-(4-Chloro-benzenesulfonylamino)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester;

6-{4-[(4-Hydroxy-2-oxo-7-trifluoromethyl-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid methyl ester;

7-{4-[(7-Acetylamino-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-heptanoic acid methyl ester;

8-(4-{[7-(4-Chloro-phenylcarbamoyl)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester;

4-Hydroxy-3-[4-(7-methoxycarbonyl-heptyloxy)-phenylcarbamoyl]-2-oxo-1,2-dihydro-quinoline-7-carboxylic acid methyl ester;

8-[4-({7-[2-(4-Chloro-phenyl)-acetylamino]-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl}-amino)-phenoxy]-octanoic acid methyl ester;

6-{4-[(7-Cyano-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid methyl ester;

6-{4-[(4-Hydroxy-2-oxo-6-phenylethynyl-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid methyl ester;

8-{4-[(4-Hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester.

Example 2: Conversion of one compound of General Formula (Ia) into another compound of Formula (Ia)

Example 2A. 8-{4-[(6-Benzo[b]thiophen-3-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid

To a suspension of 8-{4-[(6-benzo[b]thiophen-3-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester (417mg) in THF (5mL) was added a solution of NaOH (86mg) in H_2O (3mL). Methanol (4mL) was added to aid dissolution. The reaction mixture was stirred at room temperature for 4 hours and then poured onto ice/dilute HCl and the precipitate collected by filtration to yield the title compound as a white solid (400mg).

The following compounds were prepared in an analogous manner from the appropriate ester:

10-(4-{[6-(4-Chloro-phenyl)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-decanoic acid;

6-(4-{[6-(4-Fluoro-benzoylamino)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-hexanoic acid;

6-{4-[(4-Hydroxy-2-oxo-6-pentyl-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid;

10-(4-{[6-(4-Chloro-benzyloxy)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-decanoic acid;

10-(4-{[4-Hydroxy-6-(4-methoxy-phenoxy)-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-decanoic acid;

7-{4-[(4-Hydroxy-7-nitro-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-heptanoic acid;

8-{4-[(4-Hydroxy-6-iodo-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid;

8-(4-{[6-(4-Chloro-benzenesulfonylamino)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-octanoic acid;

6-{4-[(4-Hydroxy-2-oxo-7-trifluoromethyl-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid;

7-{4-[(7-Acetylamino-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-heptanoic acid;

8-(4-{[7-(4-Chloro-phenylcarbamoyl)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-octanoic acid;

3-[4-(7-Carboxy-heptyloxy)-phenylcarbamoyl]-4-hydroxy-2-oxo-1,2-dihydro-quinoline-7-carboxylic acid methyl ester;

8-[4-({7-[2-(4-Chloro-phenyl)-acetylamino]-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl}-amino)-phenoxy]-octanoic acid;

6-{4-[(7-Cyano-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid;

6-{4-[(4-Hydroxy-2-oxo-6-phenylethynyl-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid;

8-{4-[(4-Hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid.

Example 2B. 8-{4-[(5-Amino-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid

A mixture of 8-{4-[(4-hydroxy-5-nitro-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid (0.2 mmol), ammonum formate (5 eq), and Pd/C (cat) in MeOH/ H_2O (5 ml, 4:1) was heated at 60 °C for 0.30 min. The mixture was diluted with ethyl acetate and washed with water. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated in vacuo to yield the desired title compound.

Reference Example 4: Preparation of Compounds of General Formula (IIIb)

N-Methoxycarbonylmethyl-N-p-tolyl-malonamic acid methyl ester

A mixture of methyl bromoacetate (21.2mL), p-toluidine (20g) and sodium acetate (18.4g) in dry ethanol (100mL) was heated to reflux for 1 hour. The reaction mixture was then cooled and poured onto ice/water. A precipitate was produced which was collected by filtration and recrystallised from ethyl acetate/hexane to yield p-tolylamino-acetic acid methyl ester as a beige solid (16.3g)

To a cold (0°C) solution of p-tolylamino-acetic acid methyl ester (10.57g) in dry dichloromethane (100mL) was added triethylamine (9.9mL), and a solution of methyl malonyl chloride (7.60mL) in dichloromethane (20mL). After 2 hours the reaction mixture was diluted with dichloromethane, washed with sodium carbonate solution, dried

($MgSO_4$) and the solvent removed *in vacuo* to yield N-methoxycarbonylmethyl-N-p-tolyl-malonamic acid methyl ester as a yellow oil (16.1g).

In an analogous manner the following compounds of formula (IIIb) may be prepared by using the appropriately substituted aniline

N-(Phenyl)-N-methoxycarbonylmethyl-malonamic acid methyl ester was prepared from aniline;

N-(4-Chloro-phenyl)-N-methoxycarbonylmethyl-malonamic acid methyl ester was prepared from 4-chloroaniline;

N-Methoxycarbonylmethyl-N-(4-methoxy-phenyl)-malonamic acid methyl ester was prepared from p-anisidine;

N-Methoxycarbonylmethyl-N-(4-nitro-phenyl)-malonamic acid methyl ester was prepared from 4-nitroaniline;

N-Methoxycarbonylmethyl-N-naphthalen-1-yl-malonamic acid methyl ester was prepared from 1-aminonaphthalene;

N-Methoxycarbonylmethyl-N-(4-trifluoromethyl-phenyl)-malonamic acid methyl ester was prepared from 4-(trifluoromethyl)aniline;

N-Methoxycarbonylmethyl-N-(4-methyl-biphenyl-3-yl)-malonamic acid methyl ester was prepared from 5-phenyl-*o*-toluidine;

N-(4-Acetylamino-phenyl)- N-methoxycarbonylmethyl-malonamic acid methyl ester was prepared from 4'-aminoacetanilide;

N-(4-Benzo[b]thiophen-2-yl-phenyl)-N-methoxycarbonylmethyl-malonamic acid methyl ester was prepared from 4-benzo[b]thiophen-2-yl-phenylamine.

4-Benzo[b]thiophen-2-yl-phenylamine was prepared according to the following procedure.

A mixture of 4-iodoaniline (2.5 g, 11.2 mmol), 2-benzothio-pheneboronic acid (2.0 g, 11.2 mmol) and sodium carbonate (1.2 g, 11.2 mmol) in toluene (60 mL), ethanol (10 mL) and water (1 mL) was degassed with nitrogen for 5 min. A catalytic amount of $Pd(dppf)_2Cl_2$ was added, and the mixture was heated to reflux for 3 h. The mixture was cooled, adsorbed onto silica gel and purified by flash chromatography to give 4-benzo[b]thiophen-2-yl-phenylamine;

N-(4-Cyclohexyl-phenyl)-N-methoxycarbonylmethyl-malonamic acid methyl ester was prepared from 4-cyclohexylaniline;

N-(4-Benzyl-phenyl)-N-methoxycarbonylmethyl-malonamic acid methyl ester was prepared from 4-benzylaniline;

3-(Methoxycarbonylacetyl-methoxycarbonylmethyl-amino)-benzoic acid methyl ester was prepared from methyl 3-aminobenzoate;

N-Methoxycarbonylmethyl-N-(4-phenoxy-phenyl)-malonamic acid methyl ester was prepared from 4-phenoxyaniline;

2-(Methoxycarbonylacetyl-p-tolyl-amino)-propionic acid methyl ester was prepared from p-toluidine and using methyl 2-bromoprpionate instead of methyl bromoacetate;

N-[4-(4-Fluoro-benzyloxy)-phenyl]-N-methoxycarbonylmethyl-malonamic acid methyl ester was prepared from 4-(4-fluoro-benzyloxy)-phenylamine;

N-(Methoxycarbonyl-phenyl-methyl)-N-phenyl-malonamic acid methyl ester was prepared from phenyl-phenylamino-acetic acid methyl ester which was prepared by

reaction of aniline and methyl α-bromophenyl acetate in acetonitrile with potassium carbonate at reflux;

N-Benzyl-N-ethoxycarbonylmethyl-malonamic acid methyl ester was prepared from N-benzyl glycine ethyl ester (commercially available)

Reference Example 5: Preparation of Compounds of General Formula (IIb)

4-Hydroxy-2-oxo-1-p-tolyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester

To a solution of N-methoxycarbonylmethyl-N-p-tolyl-malonamic acid methyl ester (16.1g) in dry methanol (150mL) was added a 25% solution of sodium methoxide in methanol (26.4mL). The reaction mixture was heated to reflux for two hours. After cooling the reaction mixture was poured onto ice/dilute HCl yielding a white precipitate which was collected by filtration. Hot trituration from a mixture of methanol and ethyl acetate yielded the title compound as a white solid (11.25g)

In an analogous manner the following compounds of formula (IIb) may be prepared by using the appropriate compounds of formula (IIIb)

1-(Phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

1-(4-Chloro-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

4-Hydroxy-1-(4-methoxy-phenyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

4-Hydroxy-1-(4-nitro-phenyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

4-Hydroxy-1-naphthalen-1-yl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

4-Hydroxy-2-oxo-1-(4-trifluoromethyl-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

4-Hydroxy-1-(4-methyl-biphenyl-3-yl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

1-(4-Acetylamino-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

1-(4-Benzo[b]thiophen-2-yl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

1-(4-Cyclohexyl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

1-(4-Benzyl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

4-Hydroxy-1-(3-methoxycarbonyl-phenyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

4-Hydroxy-2-oxo-1-(4-phenoxy-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

4-Hydroxy-5-methyl-2-oxo-1-p-tolyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

1-[4-(4-Fluoro-benzyloxy)-phenyl]-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

4-Hydroxy-2-oxo-1,5-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester;

1-Benzyl-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester.

Example 3: Preparation of Compounds of General Formula (Ib)

8-{4-[(4-Hydroxy-2-oxo-1-p-tolyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester

A mixture of 4-hydroxy-2-oxo-1-p-tolyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid methyl ester (140mg) and 8-(4-amino-phenoxy)-octanoic acid methyl ester (160mg) in m-xylene (2mL) was heated to reflux for 2 hours. The reaction mixture was then cooled, diluted with hexane and the solid collected by filtration and washed with ether to yield the title compound as an off-white solid (140mg)

In an analogous manner the following compounds of formula (Ib) may be prepared by using the appropriate compounds of formula (IIb) and the appropriate compound of formula (IV)

8-{4-[(4-Hydroxy-2-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester;

8-(4-{[1-(4-Chloro-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester;

8-(4-{[4-Hydroxy-1-(4-methoxy-phenyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester;

2,4-Dioxo-1-p-tolyl-pyrrolidine-3-carboxylic acid {4-[7-(1H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide;

1-(4-Chloro-phenyl)-2,4-dioxo-pyrrolidine-3-carboxylic acid {4-[7-(2H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide;

1-(4-Methoxy-phenyl)-2,4-dioxo-pyrrolidine-3-carboxylic acid {4-[7-(2H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide;

8-(4-{[1-(4-Nitro-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester;

8-{4-[(4-Hydroxy-1-naphthalen-1-yl-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester;

8-(4-{[4-Hydroxy-2-oxo-1-(4-trifluoromethyl-phenyl)-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester;

8-(4-{[4-Hydroxy-1-(4-methyl-biphenyl-3-yl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester;

8-(4-{[1-(4-Acetylamino-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester;

8-(4-{[1-(4-Benzo[b]thiophen-2-yl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester;

8-(4-{[1-(4-Cyclohexyl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester;

8-(4-{[1-(4-Benzyl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester;

3-(4-Hydroxy-3-{[4-(7-methoxycarbonyl-heptyloxy)-phenylamino]-methyl}-2-oxo-2,5-dihydro-pyrrol-1-yl)-benzoic acid methyl ester;

8-(4-{[4-Hydroxy-2-oxo-1-(4-phenoxy-phenyl)-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-decanoic acid methyl ester;

8-{4-[(4-Hydroxy-5-methyl-2-oxo-1-p-tolyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester;

1-[4-(4-Fluoro-benzyloxy)-phenyl]-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid {4-[7-(1H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide;

8-{4-[(4-Hydroxy-2-oxo-1,5-diphenyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester;

8-{4-[(1-Benzyl-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester;

Example 4: Conversion of one compound of General Formula (Ib) into another compound of Formula (Ib)

8-{4-[(4-Hydroxy-2-oxo-1-p-tolyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid

To a solution of 8-{4-[(4-hydroxy-2-oxo-1-p-tolyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester (140mg) in THF (3mL) was added a solution of NaOH (35mg) in H_2O (1mL). Methanol (2mL) was added to aid dissolution. The reaction mixture was stirred at room temperature for24 hours and then acidified (HCl, 2M). The reaction mixture was extracted into ethyl acetate, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a dark solid. This was recrystallised from ethyl acetate/hexane to yield the title compound as an off white solid (88mg)

The following compounds were prepared in an analogous manner from the appropriate ester;

8-{4-[(4-Hydroxy-2-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid;

8-(4-{[1-(4-Chloro-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid;

8-(4-{[4-Hydroxy-1-(4-methoxy-phenyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid;

8-(4-{[1-(4-Nitro-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid;

8-{4-[(4-Hydroxy-1-naphthalen-1-yl-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid;

8-(4-{[4-Hydroxy-2-oxo-1-(4-trifluoromethyl-phenyl)-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid;

8-(4-{[4-Hydroxy-1-(4-methyl-biphenyl-3-yl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid;

8-(4-{[1-(4-Acetylamino-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid;

8-(4-{[1-(4-Benzo[b]thiophen-2-yl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid;

8-(4-{[1-(4-Cyclohexyl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid;

8-(4-{[1-(4-Benzyl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid;

3-{3-[4-(7-Carboxy-heptyloxy)-phenylcarbamoyl]-4-hydroxy-2-oxo-2,5-dihydro-pyrrol-1-yl}-benzoic acid methyl ester;

8-(4-{[4-Hydroxy-2-oxo-1-(4-phenoxy-phenyl)-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-decanoic acid;

8-{4-[(4-Hydroxy-5-methyl-2-oxo-1-p-tolyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid.

8-{4-[(4-Hydroxy-2-oxo-1,5-diphenyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid;

8-{4-[(1-Benzyl-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid

Example 5: Testing of the present compounds as PAI inhibitors

The present compounds were tested in a PAI-1 functional assay. In this assay, a compound is incubated with PAI-1 prior to addition to the tPA assay system. Inhibition of PAI-1 by compounds of Formula (I) prevented inhibition by PAI-1 of the enzymatic activity of tPA. In turn, tPA cleaved the chromogenic substrate Pefachrome (CH_3SO_2-D-HHT-Gly-Arg-pNA) (Centerchem, Inc) producing pNA (p-nitroaniline) which was detected spectrophotometrically at 405 nm (K.Nilsson *et al*, Fibrinolysis (1987) 1, 163-168). This is referred to as the chromogenic assay. The degrees of inhibition observed in the chromogenic substrate assay at various concentrations, or the IC_{50} values, for each compound are presented in the table below.

A selection of the present compounds were also tested in a clot lysis assay that can quantify the PAI-1 inhibitory activity of the compounds by measuring the rate of fibrinolysis (Ehnebom J, Kristianssen C, Bjorquist P, Deinum J, Bostrum S. Thrombosis

and Haemostasis, 1993, 69, 1330a). This is referred to as the fibrin plate assay. In this assay fibrinogen was clotted with thrombin and calcium to give an opaque, insoluble fibrin gel. The gel or clot contained added plasminogen and tissue plasminogen activator (tPA). tPA converted plasminogen into plasmin, and plasmin was then able to degrade the fibrin clot to form soluble fibrin fragments. This process was monitored by measuring absorbance. The addition of PAI-1 to the reaction inhibited tPA cleavage of plasminogen to plasmin and therefore inhibited clot lysis. Preincubation of the present compounds with PAI-1 inhibited PAI-1 activity thus allowing tPA to cleave plasminogen to plasmin and lyse the fibrin clot.

The biological activities of the compounds in the chromogenic assay were in the range 0.1 to 50μM as shown in the table below.

Chromogenic assay	
Compound No.	**IC_{50}(μM)**
2	0.9
3	0.97
5	2.0
6	0.68
7	10.0
8	1.0
9	3.7
10	0.35
11	2.2
12	4.25
13	4.0
14	1.7
15	3.0
17	0.23
18	0.33
19	3.25
20	1.3
21	1.65
23	8.0
24	>50
26	0.5

28	0.91
29	2.6
30	1.1
31	0.65
33	1.7
34	>50
35	2.5
36	>50
37	26.3
38	1.23
39	1.4
40	0.4
41	4.35
42	1.05
43	7.7

The biological activities of the compounds in the fibrin plate assay were in the range as shown in the table below

Fibrin plate assay	
Compound No.	**$IC_{50}(\mu M)$**
1	0.270
2	0.240
3	0.290
30	0.045
31	0.035
32	0.140

Example 6: Characterisation of the present compounds

The compounds prepared in the preceding Examples were characterised by proton N.M.R spectroscopy and mass spectroscopy. All proton N.M.R were performed at 300 or 400MHz. Characterisation by mass spectroscopy was performed using desorption chemical ionisation or electrospray ionisation. The results are set out in Table 2:

Table 2

Compound No.	Molecular formula	Mass spec. data	^{1}H NMR data
1	C32H30N6O4S	ESI-ve M-H-593	d6-DMSO 12.45(1H,s,broad), 12.18(1H,s,broad), 8.18(1H,s), 8.10(1H,dd), 8.01(1H,dd), 7.95(1H,s), 7.89(1H,dd), 7.60-7.55(3H,m), 7.52-7.45(2H,m), 6.95(2H,d), 3.95(2H,t), 2.85(2H,t), 1.72-1.65(4H,m), 1.45-1.25(6H,m) Two NH/OH not visible
2	C32H30N6O4S	CI +ve, MH+ 595 (100%)	d6-DMSO 15.75(1H,s,broad), 12.40(1H,s,broad), 12.20(1H,s,broad), 8.25(1H,s), 8.15(1H,dd), 7.99(1H,d), 7.91(1H,s), 7.85(1H,d), 7.55(2H,d), 7.50(1H,d), 7.41-7.35(2H,m), 6.95(2H,d), 3.95(2H,t), 2.86(2H,t), 1.75-1.65(4H,m), 1.45-1.25(6H,m) .One NH not visible
3	C32H30N2O6S	EI -ve M-H-569 (100)	DMSO 15.8(1H,s), 12.48(1H,s), 12.2(1H,s), 11.95(1H,s), 8.15(1H,s), 8.09(1H,s), 8.00-7.88(3H,m), 7.60-7.55(3H,m), 7.48-7.42(2H,m), 6.97(2H,d), 3.96(2H,t), 2.20(2H,t), 1.75-1.70(2H,m), 1.55-1.25(8H,m)
4	C33H32N2O6S		DMSO 15.8(1H,s), 12.48(1H,s), 12.2(1H,s), 8.15(1H,s), 8.09(1H,s), 8.00-7.86(3H,m), 7.61-7.55(3H,m), 7.48-7.42(2H,m), 6.97(2H,d), 3.96(2H,t), 3.60 (3H,s),2.26(2H,t), 1.75-1.70(2H,m), 1.55-1.25(8H,m)
11	C24H25IN2O6	FD+ m/z 564 (100%)	DMSO 1.25-1.60 (8H,m), 1.65-1.75(2H,m), 2.20(2H,t), 3.95(2H,t), 6.95(2H,d), 7.20(1H,d), 7.55(2H,d), 7.95(1H,dd), 8.20(1H,d), 11.95(1H,s), 12.10(1H,s), 12.35(1H,s), 16.7(1H,s).
17	C26H28N2O8	ES+ m/z 496 (M+,100%)	DMSO 1.20-1.55 (8H,m), 1.65-1.75(2H,m), 2.20(2H,t), 3.93(3H,s), 3.95(2H,t), 6.95(2H,d), 7.50(2H,d), 7.75(1H), 7.95(1H), 8.05(1H), 12.0(1H,s), 12.20(1H,s), 12.40(1H,s), 16.75(1H,s).
19	C23H21N3O6	ES+ m/z 435 (M+,26%)	DMSO 1.35-1.50 (2H,m), 1.50-1.60(2H,m), 1.60-1.70(2H,m), 2.25(2H,t), 3.95(2H,t), 6.90(2H,d), 7.50(2H,d), 7.55-7.70(2H,m), 8.05(1H,d), 12.0(1H,s), 12.2-12.4(2H,m), 16.60(1H,s, broad).
7	C27H32N2O6	FD+ m/z 480 (100%)	DMSO 0.85(3H,t), 1.20-1.40(4H,m), 1.40-1.50(2H,m), 1.50-1.65(4H,m), 1.65-1.75(2H,m), 2.25(2H,t), 2.65(2H,t), 3.95(2H,t), 6.95(2H,d), 7.35(1H,d), 7.50-

			7.57(3H,m), 7.85(1H,s), 11.95(1H,s), 12.50(1H,s), 16.60(1H,s). One OH not visible
10	C23H23N3O8	FD+ m/z 469.4 (100%)	DMSO 1.27-1.60 (6H,m), 1.65-1.75(2H,m), 2.22(2H,t), 3.95(2H,t), 6.95(2H,d), 7.55(2H,d), 8.05(1H,dd), 8.17-8.22(2H,m), 11.95(1H,s), 12.25(1H,s), 12.40(1H,s), 16.80(1H,s).
12	C24H27N3O6	ES+ m/z 453 (M+,100%)	DMSO 1.25-1.45(6H,m), 1.45-1.60(2H,m), 1.65-1.75(2H,m), 2.22(2H,t), 3.95(2H,t), 6.35-6.40(2H,m), 6.70(2H,s, broad), 6.95(2H,d), 7.25-7.30(1H,m), 7.50(2H,d), 11.51(1H,s), 11.95(1H,s), 12.55(1H,s). One OH not visible
14	C23H21F3N2O6	ES+ m/z 478 (M+,100%)	DMSO 1.35-1.50 (2H,m), 1.50-1.65(2H,m), 1.65-1.75(2H,m), 2.25(2H,t), 3.90(2H,t), 6.85(2H,d), 7.35(1H,d), 7.55(1H,s), 7.60(2H,d), 8.20(1H,d), 10.90(1H,s,broad), 13.20(1H,s). Two NH/OH not visible
5	C32H33ClN2O6	FD+ m/z 576 (100%)	DMSO 1.25-1.45(10H,m), 1.45-1.60(2H,m), 1.65-1.75(2H,m), 2.22(2H,t), 3.90(2H,t), 6.90(2H,d), 7.45-7.60(5H,m), 7.75(2H,d), 8.00(1H,d), 8.15(1H,s), 11.95(1H,s), 12.10(1H,s), 12.40(1H,s), 16.75(1H,s)
15	C25H27N3O7	ES+ m/z 481 (M+,100%)	DMSO 1.30-1.45(4H,m), 1.47-1.57(2H,m), 1.65-1.75(2H,m), 2.12(3H,s), 2.22(2H,t), 3.95(2H,t), 6.95(2H,d), 7.35(1H,d), 7.55(2H,d), 7.90(1H,d), 7.95(1H,s), 10.45(1H,s), 11.95(1H,s), 12.40(1H,s), 16.55(1H,s). One OH not visible
6	C29H26FN3O7	ES+ m/z 547 (M+,75%)	DMSO 1.40-1.50 (2H,m), 1.50-1.65(2H,m), 1.65-1.75(2H,m), 2.25(2H,t), 3.95(2H,t), 6.95(2H,d), 7.35-7.45(3H,m), 7.55(2H,d), 8.05-8.10(3H,m), 8.50(1H,s), 10.50(1H,s), 12.10(1H,s), 12.55(1H,s), 16.65(1H,s). One OH not visible
21	C26H30N2O8	ES+ m/z 498 (M+,100%)	DMSO 1.25-1.45(6H,m), 1.45-1.60(2H,m), 1.65-1.75(2H,m), 2.20(2H,t), 3.85(3H,s), 3.87(3H,s), 3.95(2H,t), 6.85(1H,s), 6.90(2H,d), 7.25(1H,s), 7.50(2H,d), 11.75(1H,s), 11.95(1H,s), 12.50(1H,s), 16.45(1H,s).
8	C33H35N2O7Cl		DMSO 1.25-1.45(10H,m), 1.45-1.55(2H,m), 1.65-

			1.75(2H,m), 2.20(2H,t), 3.90(2H,t), 5.15(2H,s), 6.90(2H,d), 7.32-7.55(9H,m), 11.95(1H,s), 12.55(1H,s), 16.65(1H,s). One OH not visible
9	C33H36N2O8	FD+ m/z 588 (100%)	DMSO 1.25-1.45(10H,m), 1.45-1.55(2H,m), 1.65-1.75(2H,m), 2.20(2H,t), 3.75(3H,s), 3.90(2H,t),6.90(2H,d), 7.00(2H,d), 7.07(2H,d), 7.27(1H,s), 7.35-7.45(2H,m), 7.55(2H,d), 11.95(1H,s,broad), 12.02(1H,s), 12.50(1H,s), 16.70(1H,s).
13	C30H30ClN3O8S	ES+ m/z 627 (M+,100%)	DMSO 1.25-1.45(6H,m), 1.45-1.60(2H,m), 1.65-1.75(2H,m), 2.20(2H,t), 3.95(2H,t), 6.95(2H,d), 7.32(1H,d), 7.48-7.52(3H,m), 7.62-7.70(3H,m), 7.75(2H,d), 10.52(1H,s), 12.02(1H,s), 12.42(1H,s), 16.60(1H,s). One OH not visible.
16	C31H30ClN3O7	FD+ m/z 591 (100%)	DMSO 1.25-1.45(6H,m), 1.47-1.57(2H,m), 1.65-1.75(2H,m), 2.20(2H,t), 3.95(2H,t), 6.75(1H,dd), 7.15(1H,d), 7.25-7.35(2H,m), 7.45(2H,d), 7.75-7.85(3H,m), 7.90(1H,s), 8.12(1H,d), 10.65(1H,s), 11.95(1H,s), 12.28(1H,s), 12.56(1H,s), 16.60(1H,s).
18	C32H32ClN3O7	ES+ m/z 605 (M+,100%)	DMSO 1.25-1.45(6H,m), 1.47-1.57(2H,m), 1.65-1.75(2H,m), 2.20(2H,t), 3.75(2H,s), 3.95(2H,t), 6.95(2H,d), 7.35-7.42(5H,m), 7.55(2H,d), 7.91-7.96(2H,m), 10.70(1H,s), 11.9-12.0(2H,m), 12.40(1H,s), 16.55(1H,s).
20	C30H26N2O6	FD+ m/z 510 (100%)	DMSO 1.40-1.50 (2H,m), 1.50-1.65(2H,m), 1.65-1.75(2H,m), 2.25(2H,t), 3.95(2H,t), 6.95(2H,d), 7.35-7.60(8H,m), 7.80(1H,dd), 8.00(1H,d), 12.00(1H,s), 12.18(1H,s), 12.30(1H,s), 16.70(1H,s).
22	C26H30N2O6	DCI+NH3 MH+467 MHN4+484	DMSO 10.12 (1H, s), 7.71 (2H, d), 7.53 (2H, d), 7.38 (2H, t), 7.11 (1H, t), 6.90 (2H, d), 4.58 (2H, s), 3.93 (2H, t), 3.57 (3H, s), 2.29 (2H, t), 1.72-1.65 (2H, m), 1.56-1.49 (2H, m), 1.39-1.35 (2H, m), 1.31-1.29 (4H, m)
23	C25H28N2O6	DCI+NH3 MH+453 MNH4+470	d6-dmso 10.18 (1H, s), 7.71 (2H, d), 7.52 (2H, d), 7.37 (2H, t), 7.10 (1H, t), 6.89 (2H, d), 4.52 (2H, s), 3.93 (2H, t), 2.19 (2H, t), 1.76 - 1.67 (2H, m), 1.52 - 1.48 (2H, m), 1.43 - 1.36 (2H, m), 1.35 - 1.25 (4H, m)
24	C26H29ClN2O6	MS DCI+/NH3 m/e 501/503	d6-DMSO 1.25-1.45(6H,m), 1.49-1.55(2H,m), 1.65-

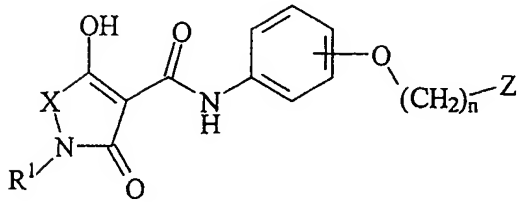
		(MH+,20/8)	1.72(2H,m), 2.29(2H,t), 3.57(3H,s), 3.93(2H,t), 4.57(2H,s), 6.90(2H,d), 7.41-7.45(2H,m), 7.50-7.54(2H,m), 7.73(2H,m), 10.08(1H,s). One NH/OH not visible
25	C27H32N2O7	MS DEI+ m/e 496(M+, 50%)	d6-DMSO 1.25-1.45(6H,m), 1.49-1.55(2H,m), 1.65-1.72(2H,m), 2.29(2H,t), 3.57(3H,s), 3.72(3H,s), 3.93(2H,t), 4.57(2H,s), 6.90(2H,d), 6.95(2H,d), 7.52(2H,d), 7.57(2H,d), 10.10(1H,s). One NH/OH not visible
26	C25H27ClN2O6	MS DCI/NH3 m/e 487/489 (MH+ 100/40).	D6-DMSO 1.25-1.42(6H,m), 1.48-1.52(2H,m), 1.65-1.71(2H,m), 2.20(2H,t), 3.94 (2H,t), 4.55(2H,s), 6.90 (2H,d), 7.43(2H,d), 7.54 (2H,d), 7.75 (2H,d), 10.21 (1H,s) Two OH not visible
27	C27H32N2O6	MS DEI+ m/z 480(M+,40%).	D6-DMSO 1.23-1.42 (6H,m), 1.48-1.53 (2H,m), 1.65-1.71 (2H,m), 2.25-2.30(5H,m, methyl singlet overlapping triplet), 3.55(s, 3H), 3.90 (2H,t), 4.52 (2H,s), 6.89(2H,d), 7.17(2H,d), 7.52 (2H,d), 7.60(2H,d), 10.14 (1H,s). One NH/OH not visible
28	C26H30N2O6	DCI+/NH3 m/e 467(MH+, 30%).	D6-DMSO 1.25-1.42 (6H,m), 1.45-1.52 (2H,m), 1.65-1.71 (2H,m), 2.18 (2H,t), 2.28 (3H,s), 3.92 (2H,t), 4.55(2H,s), 6.90 (2H,d), 7.18(2H,d), 7.52 (2H,d), 7.58(2H,d), 10.15 (1H,s). Two OH not visible
29	C26H30N2O7	MS DEI+ m/e 482 (M+,40%)	D6-DMSO 1.25-1.43(6H,m), 1.45-1.52(2H,m), 1.65-1.71(2H,m), 2.18(2H,t), 3.75(3H,s), 3.93(2H,t), 4.55(2H,s), 6.90(2H,d), 6.95(2H,d), 7.52(2H,d), 7.58(2H,d), 10.14(1H,s). Two OH not visible
30	C26H30N6O4	ESI m/z 491 (MH+, 6%), 447 ([M-43]+, 100%)	d6-dmso 9.20 (1H, s); 7.54 (2H, d); 7.11 (4H, m); 6.91 (2H, d); 5.16 (1H, s); 4.49 (2H, s); 3.92 (2H,t); 2.87 (2H, t); 2.25 (3H, s); 1.69 (4H, m); 1.36 (6H,m).
31	C25H27ClN6O4	No molecar ion. ESI -ve 465 (100%, M-H for molecular ion less 44)	d6-dmso 1.25-1.46(6H,m), 1.6-1.78(4H,m), 2.81-2.92(2H,t), 3.89-3.98(2H,t), 4.5-4.59(2H,s), 5.16-5.22(1H,s), 6.88-6.99(2H,d), 7.1-7.18(2H,d), 7.31-7.4(2H,d), 7.67-7.72(2H,m), 9.27-9.32(NH, s)
32	C26H30N6O5	No molecular ion. (M-43)+ as for 11831 and	D6-DMSO 9.15(1H,s), 7.55(2H,d), 7.10(2H,d), 6.92-6.88(4H,m), 5.16(1H,s), 4.46(2H,s), 3.92(2H,t),

		4477	3.72(3H,s), 2.88(2H,t), 1.75-1.65(4H,m), 1.45-1.28(6H,m). One NH not visible
41	C27H30N2O8	ES+ m/z 510 (M+,100%)	D6-DMSO 1.30-1.45(6H,m), 1.45-1.60(2H,m), 1.60-1.75(2H,m), 2.20(2H,t), 3.75-3.95(5H,m), 4.02(2H,s), 6.80(2H,d), 7.40-7.45(1H,m), 7.52-7.57(3H,m), 7.90(1H,d), 8.45(1H,s), 10.78(1H,s), Two NH/OH not visible
39	C31H38N2O6	FD+ m/z 534 (100%)	d6-DMSO 1.15-1.45(11H,m), 1.45-1.50(2H,m), 1.65-1.85(7H,m), 2.20(2H,t), 2.40-2.45(1H,m), 3.90(2H,t), 4.57(2H,s), 6.90(2H,d), 7.20(2H,d), 7.55(2H,d), 7.60(2H,d), 10.07(1H,s). Two NH/OH not visible
40	C32H34N2O6	FD+ m/z 542 (100%)	D6-DMSO 1.23-1.45(6H,m), 1.45-1.60(2H,m), 1.60-1.75(2H,m), 2.20(2H,t), 3.90-3.96(4H,m), 4.57(2H,s), 6.90(2H,d), 7.15-7.30(7H,m), 7.55(2H,d), 7.62(2H,d), 10.12(1H,d). Two NH/OH not visible
37	C27H31N3O7	ES+ m/z 509 (M+,100%)	D6-DMSO 1.23-1.45(6H,m), 1.45-1.60(2H,m), 1.60-1.75(2H,m), 2.05(3H,s), 2.20(2H,t), 3.95(2H,t), 4.55(2H,s), 6.90(2H,d), 7.52-7.65(6H,m), 9.95(1H,s) 10.12(1H,d). Two NH/OH not visible
35	C26H27F3N2O6	ES+ m/z 520 (M+,100%)	D6-DMSO 1.23-1.45(6H,m), 1.45-1.60(2H,m), 1.60-1.75(2H,m), 2.20(2H,t), 3.95(2H,t), 4.64(2H,s), 6.90(2H,d), 7.56(2H,d), 7.74(2H,d), 7.95(2H,d), 10.03(1H,s). Two NH/OH not visible
33	C25H27N3O8	FD+ m/z 497 (M+,60%), 453(100%)	D6-DMSO 1.23-1.45(6H,m), 1.45-1.60(2H,m), 1.60-1.75(2H,m), 2.20(2H,t), 3.95(2H,t), 4.64(2H,s), 6.90(2H,d), 7.56(2H,d), 7.95(2H,d), 8.27(2H,d), 10.03(1H,s). Two NH/OH not visible
34	C29H30N2O6	ES+ m/z 502 (M+,100%)	D6-DMSO 1.24-1.48(6H,m), 1.50-1.60(2H,m), 1.60-1.75(2H,m), 2.20(2H,t), 3.95(2H,t), 4.64(2H,s), 6.90(2H,d), 7.50(2H,d), 7.55-7.62(4H,m), 7.75-7.80(1H,m), 7.97-8.03(2H,m), 10.13(1H,s). Two NH/OH not visible
36	C32H34N2O6	ES+ m/z 542 (M+,100%)	D6-DMSO 1.24-1.42(6H,m), 1.46-1.60(2H,m), 1.60-1.75(2H,m), 2.20(2H,t), 2.25(3H,s), 3.95(2H,t), 4.64(2H,s), 6.90(2H,d), 7.35-7.60(7H,m), 7.67-7.72(3H,m), 10.18(1H,s). Two NH/OH not visible

38	C33H32N2O6S	FD+ m/z 584 (M+,10%), 540(100%)	D6-DMSO 1.24-1.42(6H,m), 1.46-1.60(2H,m), 1.60-1.75(2H,m), 2.20(2H,t), 3.95(2H,t), 4.64(2H,s), 6.90(2H,d),7.30-7.42(2H,m), 7.55(2H,d), 7.75-7.85(6H,m), 7.95(1H,d), 10.20(1H,s). Two NH/OH not visible
42	C33H36N2O7	ES+ m/z 573 (MH+, 100%)	D6-DMSO 1.25-1.46(10H,m), 1.47-1.55(2H,m), 1.60-1.75(2H,m), 2.20(2H,t), 3.92(2H,t), 4.60(2H,s), 6.85-7.15(7H,m), 7.35(2H,d), 7.55(2H,d), 7.75(2H,d), 10.15(1H,s). Two NH/OH not visible
43	C27H32N2O6	ES+ m/z 480 (100%)	DMSO 1.25-1.45(9H,m), 1.46-1.58(2H,m), 1.62-1.75(2H,m), 2.20(2H,t), 2.30(3H,s), 3.95(2H,t), 5.02(1H,d), 6.90(2H,d), 7.22(2H,d), 7.42(2H,d), 7.55(2H,d), 10.12(1H,s). Two NH/OH not visible
44	C32H33FN6O5	ES+ m/z 600 (M+, 100%)	DMSO 1.30-1.45(6H,m), 1.60-1.75(4H,m), 2.85(2H,t), 3.92(2H,t), 4.57(2H,s), 5.08(2H,s), 6.90(2H,d), 7.02(2H,d), 7.18-7.26(2H,t), 7.46-7.56(4H,m), 7.60(2H,d), 10.17(1H,s). Two NH/OH not visible
45	C31H32N2O6	DCI+NH3 MH+ 529	DMSO 10.25 (1H,s,broad), 7.57-7.50 (4H,m), 7.31-7.30 (4H,m), 7.26-7.22 (3H,m), 7.02-6.96 (1H, m), 6.89 (2H, d), 5.91(1H,s), 3.92 (2H, t), 2.19 (2H,t), 1.73-1.66 (2H,m), 1.53 - 1.46 (2H, m), 1.42 - 1.34 (2H, m), 1.33 - 1.28 (3H, m), 1.24 - 1.22 (1H, m) Two NH/OH not visible
46	C26H30N2O6	DCI+NH3 MH+ 467	D6-dmso 10.18 (1H, s), 7.73 (2H, d), 7.52 (2H, d), 7.40 (2H, t), 7.10 (1H, t), 6.89 (2H, d), 4.52 (2H,s), 3.98(2H,s), 3.93 (2H, t), 2.19 (2H, t), 1.76 - 1.67 (2H, m), 1.52 - 1.48 (2H, m), 1.43 - 1.36 (2H, m), 1.35 - 1.25 (4H, m). Two NH/OH not visible

CLAIMS

1. A compound which is a cyclic amide of formula (I):



I

wherein X is CHR^2 or $-C(R^3)=C(R^4)-$ wherein R^2 is H, C_1-C_6 alkyl or Ar and R^3 and R^4, together with the carbon atoms to which they are attached, form a benzene ring which is unsubstituted or substituted;

R^1 is H, C_1-C_6 alkyl, $-(CH_2)_nAr$ or an unsaturated carbocyclic group which is unsubstituted or substituted;

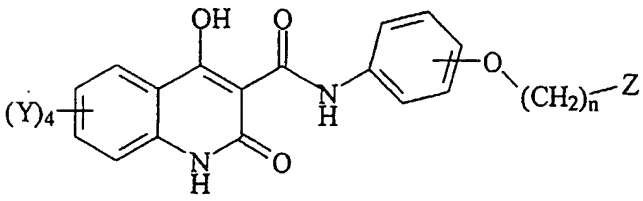
n is 1 to 10;

Ar is an unsaturated carbocyclic group or unsaturated heterocyclic group which is unsubstituted or substituted; and

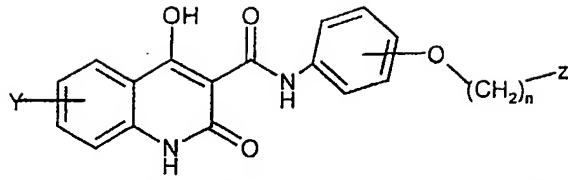
Z is tetrazole or CO_2R^5 wherein R^5 is H or C_1-C_6 alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein the cyclic amide is of formula (Ia): :



Ia



Ia

wherein each Y, which may be the same or different, is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CN, CO_2R^5 wherein R^5 is as defined in claim 1, $-O(CH_2)_pAr$, $-(Q)_pAr$, nitro, $N(R^5)_2$ wherein R^5 is as defined in claim 1, or C_1-C_6 alkyl which is unsubstituted or substituted by halogen, or is $-CONHR^6$, $-NHCOR^6$ or $-NHSO_2R^6$ wherein R^6 is C_1-C_6 alkyl or $(CH_2)_pAr$;

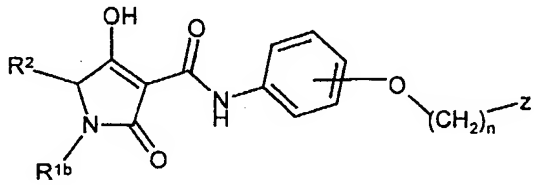
Q is a C_1-C_6 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene chain;

n is 1 to 10;

p is 0 to 6; and

Ar and Z are as defined in claim 1.

3. A compound according to claim 1 wherein the cyclic amide is of formula (Ib):



Ib

wherein R^{1b} is C_1-C_6 alkyl or $-(CH_2)_pAr$ wherein Ar is as defined in claim 1 and is unsubstituted or substituted by a group selected from C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, halogen, nitro, CO_2R^5 wherein R^5 is as defined in claim 1, $-O(CH_2)_pAr$ or $(CH_2)_pAr$ wherein Ar is as defined above, $NHCOR^6$ where R^6 is as defined in claim 1, and C_1-C_6 alkyl which is unsubstituted or substituted by halogen;

R^2 is H, C_1-C_6 alkyl or Ar as defined above;

n is 1 to 10;

p is 0 to 6; and

Z is as defined in claim 1.

4. A compound according to claim 1 which is selected from:

6-Benzo[b]thiophen-3-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid {4-[7-(2H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide

6-Benzo[b]thiophen-2-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid {4-[7-(2H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide

8-{4-[(6-Benzo[b]thiophen-3-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid

8-{4-[(6-Benzo[b]thiophen-3-yl-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester

10-(4-{[6-(4-Chloro-phenyl)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-decanoic acid

6-(4-{[6-(4-Fluoro-benzoylamino)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-hexanoic acid

6-{4-[(4-Hydroxy-2-oxo-6-pentyl-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid

10-(4-{[6-(4-Chloro-benzyloxy)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-decanoic acid

10-(4-{[4-Hydroxy-6-(4-methoxy-phenoxy)-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-decanoic acid

7-{4-[(4-Hydroxy-7-nitro-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-heptanoic acid

8-{4-[(4-Hydroxy-6-iodo-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid

8-{4-[(5-Amino-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-

octanoic acid

8-(4-{[6-(4-Chloro-benzenesulfonylamino)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-octanoic acid

6-{4-[(4-Hydroxy-2-oxo-7-trifluoromethyl-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid

7-{4-[(7-Acetylamino-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-heptanoic acid

8-(3-{[7-(4-Chloro-phenylcarbamoyl)-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino}-phenoxy)-octanoic acid

3-[4-(7-Carboxy-heptyloxy)-phenylcarbamoyl]-4-hydroxy-2-oxo-1,2-dihydro-quinoline-7-carboxylic acid methyl ester

8-[4-({7-[2-(4-Chloro-phenyl)-acetylamino]-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl}-amino)-phenoxy]-octanoic acid

6-{4-[(7-Cyano-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid

6-{4-[(4-Hydroxy-2-oxo-6-phenylethynyl-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-hexanoic acid

8-{4-[(4-Hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenoxy}-octanoic acid

8-{4-[(4-Hydroxy-2-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester

8-{4-[(4-Hydroxy-2-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid

8-(4-{[1-(4-Chloro-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester

8-(4-{[4-Hydroxy-1-(4-methoxy-phenyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid methyl ester

8-(4-{[1-(4-Chloro-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid

8-{4-[(4-Hydroxy-2-oxo-1-p-tolyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid methyl ester

8-{4-[(4-Hydroxy-2-oxo-1-p-tolyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid

8-(4-{[4-Hydroxy-1-(4-methoxy-phenyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid

2,4-Dioxo-1-p-tolyl-pyrrolidine-3-carboxylic acid {4-[7-(1H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide

1-(4-Chloro-phenyl)-2,4-dioxo-pyrrolidine-3-carboxylic acid {4-[7-(2H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide

1-(4-Methoxy-phenyl)-2,4-dioxo-pyrrolidine-3-carboxylic acid {4-[7-(2H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide

8-(4-{[1-(4-Nitro-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid

8-{4-[(4-Hydroxy-1-naphthalen-1-yl-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid

8-(4-{[4-Hydroxy-2-oxo-1-(4-trifluoromethyl-phenyl)-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid

8-(4-{[4-Hydroxy-1-(4-methyl-biphenyl-3-yl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid

8-(4-{[1-(4-Acetylamino-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid

8-(4-{[1-(4-Benzo[b]thiophen-2-yl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid

8-(4-{[1-(4-Cyclohexyl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid

8-(4-{[1-(4-Benzyl-phenyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-octanoic acid

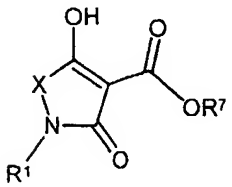
3-{3-[4-(7-Carboxy-heptyloxy)-phenylcarbamoyl]-4-hydroxy-2-oxo-2,5-dihydro-pyrrol-1-yl}-benzoic acid methyl ester

8-(4-{[4-Hydroxy-2-oxo-1-(4-phenoxy-phenyl)-2,5-dihydro-1H-pyrrole-3-carbonyl]-amino}-phenoxy)-decanoic acid

8-{4-[(4-Hydroxy-5-methyl-2-oxo-1-p-tolyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-

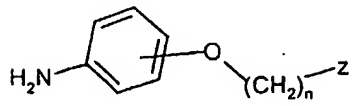
phenoxy}-octanoic acid
1-[4-(4-Fluoro-benzyloxy)-phenyl]-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid {4-[7-(1H-tetrazol-5-yl)-heptyloxy]-phenyl}-amide
8-{4-[(4-Hydroxy-2-oxo-1,5-diphenyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid
8-{4-[(1-Benzyl-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonyl)-amino]-phenoxy}-octanoic acid; and the pharmaceutically acceptable salts thereof.

5. A process for producing a compound as defined in claim 1, which process comprises reacting a compound of formula (II):



II

wherein R^7 is C_1-C_6 alkyl and X and R^1 are as defined in claim 1, with a compound of formula (IV):



IV

wherein n and Z are as defined in claim 1, in an organic solvent at an elevated temperature.

6. A process according to claim 5 which further comprises converting a resulting cyclic amide of formula (I) into another cyclic amide of formula (I), and/or converting a resulting cyclic amide of formula (I) into a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as an active principal, a compound as claimed in any one of claims 1 to 4.

8. A compound as defined in any one of claims 1 to 4 for use in a method of treatment of the human or animal body by therapy.

9. A compound as claimed in claim 8 for use as an inhibitor of PAI-1.

10. Use of a compound as claimed in any one of claims 1 to 4 in the manufacture of a medicament for use as an inhibitor of PAI-1.

11. Use according to claim 10 wherein the medicament is for use in treating a disease or disorder associated with elevated or inappropriate levels of PAI-1.

12. Use according to claim 10 or 11 wherein the medicament is for use in treating a haemostatic or thrombotic disorder.

INVESTOR IN PEOPLE

Application No:	GB 0101227.7	**Examiner:**	Darren Handley
Claims searched:	1-12	**Date of search:**	2 July 2002

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.T):

Int Cl (Ed.7): C07D 207/38, 215/22, 257/04, 333/54, 403/12, 409/04, 409/10, 409/14

Other: Online: WPI, EPODOC, JAPIO, CAS-ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
A	US 6133285 A (BJORK) - see example 8 and claim 1	
A	US 5420153 A (SCHIEHSER) - see example 3 and claim 1	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.